Remarks

The above Amendments and these Remarks are in reply to the Office action mailed February 1, 2001.

35 USC §112, First Paragraph Rejections

The Examiner has rejected claims 10 and 11 for lack of enablement. Basically, the Examiner argues that Applicants' invention is in the area of gene therapy, that such is unpredictable, and would require undue experimentation. The Examiner further states that Applicants' specification teaches gene therapy applications only by "prophetic consideration," and that the burden is on the Applicants to provide evidence that Applicants' adenoviral construct "was administered to an art accepted model, wherein a neoplastic condition was treated."

For the reasons presented in the previous amendment, Applicants respectfully disagree with the Examiner. Nevertheless, Applicants have done experiments, in an art-accepted model, to show that the invention viruses have the properties claimed. For example, Applicants have shown the in vivo activity of a claimed virus wherein the heterologous gene is cytosine deaminase (CD). The virus containing CD was directly injected into MDA-MB-231 breast carcinoma tumor xenografts grown in nude mice, followed by intraperitoneal administration of the cytosine deaminase substrate, 5-fluorocytosine. The extent of in vivo prodrug conversion of 5-fluorocytosine to 5-fluorouracil, the active chemotherapeutic agent, was determined by extraction of excised tumors from the animals and measurement of 5-fluorouracil levels using HPLC and mass spectrometry techniques. In addition, plasma levels of 5-fluorouracil were measured in

order to determine the extent of systemic exposure to the chemotherapeutic. The results showed 5-fluorouracil levels of 30 micromolar at 2 hours post 5-fluorocytosine administration from tumors injected with the invention virus. Detectable 5-fluorouracil levels in plasma reached 34.3 micromolar at 30 minutes and decreased rapidly 1 hour post 5-fluorocytosine administration. It is important to note, that these concentrations of 5-fluorouracil are above those known to achieve therapeutic benefit in cancer patients when 5-fluorouracil is administered alone. The concentration in that setting is 10 micromolar.

Based on the discussion of the data presented above, Applicants respectfully submit that the claims are enabled for the in vivo applications as described in their specification.

The Examiner has also queried what is meant by "heterologous gene" in claim 10. This phrase is well known and accepted in the art and includes any gene not naturally present in adenoviruses. Further, the Examiner will note that claim 10, as amended, depends from claims 1, 5, 6 or 15, and claim 6 recites certain specific heterologous genes.

35 USC §112, first paragraph rejections

Claims 7-9 stand rejected under §112, first paragraph for reasons previously of record. The Examiner believes that these claims are not enabled for in vivo applicability. Applicants respectfully wish to incorporate the arguments presented above, along with the showing of data to rebut the rejection. Indeed, the data show that Applicants have demonstrated in vivo applicability, and consequently, respectfully request that the rejection be withdrawn.

Claim 1 stands rejected as being indefinite. Specifically, the Examiner has stated that "essentially" renders the claim indefinite. Applicants respectfully disagree with the Examiner on this point and refer the Examiner to in re Morosi, 218 USPQ 289. Their use of the term was held acceptable in a fact profile similar to that presented in Applicants' claims. Thus, Applicants respectfully request that the rejection be withdrawn.

The Examiner will note that Applicants have added a new claim, claim 15 which recites that the "heterologous gene" is operably linked to the E1B promoter. Support for this language is found on page 12, lines 5-13 of Applicants' specification. This claim does not recite the offensive word "essentially," of claim 1.

35 USC §102 rejections

Claims 1-3, 5-10, 12-14, stand rejected under §102(b) as being anticipated by Bischoff et al. (U.S. Patent No. 6,080,578. Bischoff et al does show recombinant adenoviruses comprising an E1B deletion and that such viruses can be used for killing cancer. However, nowhere in Bischoff et al is there a showing of deleting a gene or genes from the E1B region of adenovirus, inserting a heterologous gene, and having that gene be operably linked to the E1B promoter. For a reference to be applied under §102(b), the reference must show each and every feature of that which is claimed. As that is not the case here, Applicants respectfully request that the Examiner withdraw the rejection.

In view of the above Amendments and Remarks, reconsideration of the claims is respectfully requested.

The Commissioner is authorized to charge any fees due to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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